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Original Article

Comparison of Maternal IgG Antibody from Infected SARS-CoV-2 Mothers to Newborns in the 2nd and 3rd Trimesters: A Cohort Study

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Abstract

Background: No vertical transmission has been reported for Severe Acute Respiratory Syndrome (SARS-CoV-2); Yet, Immunoglobulin G (IgG) antibody was detected against SARS-CoV-2 amongst infants. The present study aimed to compare maternal IgG antibody concentration from infected SARS-CoV-2 mothers to newborns in the 2nd and 3rd trimesters. As a secondary outcome, the interval between the onset of infection and delivery and COVID-19 severity were compared.
Methods: An observational cohort study was conducted on COVID-19 positive pregnant women in the 2nd and 3rd trimesters in Fars province, Iran between 21 March and 22 October 2021. A questionnaire was completed to record background characteristics of the study participants. Real-time Reverse Transcription Polymerase Chain Reaction tests were taken from newborns immediately after birth to diagnose COVID-19. Maternal and cord blood specimen were taken to measure IgG concentrations; generalized linear models were used to report the crude and adjusted Rate Ratios with 95% confidence interval (cRR and aRR (95% C.I)), and IBM SPSS Statistics version 22 was used, at the significance level of 0.05.
Results: From 37 patients, 15 and 22 patients were in the 2nd and 3rd trimesters of pregnancy, respectively. After adjusting on maternal age, Cord IgG concentration was positively associated with maternal IgG concentration and interval between the onset of infection and delivery in the 3rd trimester (aRR (95% CI); 2.86 (2.27-3.6) and 1.23 (1.01-1.51)); however, no association was observed with COVID-19 severity (aRR (95% CI); 0.88 (0.09-8.66)). A positive association was also seen between high levels of cord IgG and maternal IgG (≥1.1 U/mL) (aRR (95% CI); 2.31 (1.05-5.09)). No significant associations were seen in the 2nd trimester of pregnancy (P>0.05 for all).
Conclusions: In late pregnancy, Cord IgG concentration was positively associated with maternal IgG and interval between the onset of infection and delivery. Also, high levels of IgG antibody (≥1.1 U/mL) resulted in significantly higher level of cord IgG (≥1.1 U/mL).

Keywords: IgG antibody, Mother-to-child transmission, Pregnancy, SARS-CoV-2, COVID-19

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1. Introduction

In the early twentieth century, the epidemic of the Corona Virus Disease-2019 (COVID-19) was publicized in the world. COVID-19, the third zoonotic outbreak caused by Coronaviruses, was extremely infectious, and its human related clinical signs were from asymptomatic to mild, moderate, severe, and death (1). There are seven zoonotic types of Coronaviruses: NL63, 229E, HKU1, OC43, Severe Acute Respiratory Syndrome (SARS-CoV), Middle East Respiratory Syndrome (MERSE-CoV), and SARS-CoV type 2 (SARS-CoV-2). The SARS-CoV virus infected many people during 2002 and 2003; however, in comparison with SARS-CoV and MERSE-CoV, SARS-CoV-2 has been less severe in pregnant women (2). SARS-CoV-2 inducing COVID-19 caused 245,373,039 confirmed global cases up to October 29, 2021. Pregnancy, as a vulnerable period in any women's life, requires more attention devoted to both the mother and fetus (2). Due to physiological changes and immunosuppressive state, pregnant women are revealed to be more prone to SARS-CoV-2 infection (3, 4). Previous studies reported no vertical transmission for SARS-CoV-2 except for one SARS-CoV-2 positive newborn infant, born from an infected mother in Wuhan Children's Hospital in Hubai Province, China on February 5, 2020 during the COVID-19 epidemic (5, 6). It is noteworthy to

add that mother-to-child transmission becomes less frequent in late pregnancy. Moreover, no dangers have been reported for fetuses born from COVID-19 positive mothers (2, 7). The placenta has been shown to be a doorway organ in neonatal passive immunity. The passive immunity is derived from trans-placental transfer of Immunoglobulin G (IgG) antibody during pregnancy. This kind of immunity can reduce the risk of severe infections in the early post neonatal period. It is postulated that early life immunity is regulated by maternal IgG levels. Also, it has been shown that vaccination against influenza could enhance the neonatal antibody levels, and consequently protect the neonate against respiratory infections in early life (8). Additionally, IgG antibody was detected against SARS-CoV-2 amongst infants born from infected mothers (9-13). Therefore, the present study aimed to compare maternal IgG antibody concentration from infected SARS-CoV-2 mothers to newborns in the 2nd and 3rd trimesters. As a secondary outcome, the interval between the onset of infection and delivery and COVID-19 severity were compared.

2. Methods

2.1. Study design/eligibility criteria: In an observational cohort study, out of 98 laboratory-confirmed SARS-CoV-2 pregnant women reported to triple obstetrics and gynecology centers affiliated with Shiraz University of Medical Sciences, Fars province, Iran between March 21 and October 22, 2021, a total of 37 eligible mothers were entered into the study. Among these mothers, 15 were in the 2nd trimester and 22 were in the 3rd trimester. Written consent forms were taken from all the participants.

At the first COVID-19 laboratory diagnosis, a questionnaire was filled up for the participants, which involved information on maternal age, history of live birth, history of abortion, history of still birth, and COVID-19 severity. At delivery, information on Gestational Age (GA) at delivery, preterm birth, delivery type, birth weight, birth height, first-minute Apgar score, fifth-minute Apgar score, interval between the onset of infection and delivery, and sex was recorded. Maternal and cord blood specimen were also taken at delivery to measure IgG concentrations. Moreover, real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) tests were taken from newborns immediately after birth. All the mothers were asymptomatic and took no RT-PCR tests for COVID-19 at delivery.

2.2. Inclusion criteria: The inclusion criteria were: SARS-CoV-2- positive pregnant women in the 2nd and 3rd pregnancy trimesters, Body Mass Index (BMI) <35 kg/m^2, no history of underlying diseases, and no history of immunosuppressant medications consumption.

2.3. Exclusion criteria: The exclusion criteria were: a history of COVID-19 vaccination, newborn's RT-PCR positive result at delivery, and unwillingness to be followed up.

In the present observational cohort study, the starting point was the initial exposure to COVID-19. It was continued until the last follow-up when the patients delivered their newborns.

2.4. Variable definition and measurement: The maternal underlying variables were age (years), GA (weeks), history of live birth, history of abortion, history of still birth, preterm birth (no (≥37 weeks of gestation) / yes (<37 weeks of gestation)), and delivery type (Normal Vaginal Delivery (NVD) / Cesarean Section (C/S)). The newborn underlying variables were birth weight (gram), birth height (cm), first-minute Apgar score, fifth-minute Apgar score, and sex (male / female). The outcome variables were quantitative maternal IgG concentration, qualitative maternal IgG concentration (U/mL) (≥1.1 as the high level and <0.8 as the low level), quantitative cord IgG concentration (U/mL), qualitative cord IgG concentration (U/mL) (≥1.1 as the high level and <0.8 as the low level), interval between the onset of infection and delivery (weeks), and COVID-19 severity (mild and moderate / severe). It should be noted that the laboratory-confirmed SARS-CoV-2 cases were the positive cases approved by real-time RT-PCR.

To measure IgG concentrations, 3 cc blood samples were taken from both the mother and the fetal umbilical cord at delivery. The samples were centrifuged and stored at -20 - 70 °C. Maternal and cord IgG concentrations were measured by Anti-SARS-CoV-2 RBD ELISA Detection Kit.

2.5. Statistical Analysis

Median±Inter Quartile Range (IQR) and

frequency (relative frequency) were used to describe the quantitative and qualitative variables, respectively. Then, the data were analyzed via Kolmogorov-Smirnov normality test, Fisher's exact test, Chi-square test, Mann- Whitney U test, Pearson's correlation (Log_2 transformation was used to reach the normality assumption for infant's IgG concentration and mother's IgG concentration), and Linear and Poisson generalized linear models were used and adjusted Rate Ratios with 95% confidence interval (aRR (95% C.I)) were reported. Estimation of the sample size was done using MedCalc version 20.015; in addition, SPSS version 22 was used to analyze the data at significance level of 0.05.

Sample size considerations:

Cord blood IgG concentrations were positively correlated with maternal IgG concentrations among mothers infected with SARS-CoV-2 (r=0.886) (14); Given type I error= 0.05, type two error= 0.20 and using the following formula:

$$n \geq \left(\frac{z_{1-\alpha/2} + z_{1-\beta}}{0.5 * \ln\left(\frac{1+r}{1-r}\right)} \right)^2 + 3$$

with $Z_{1-\alpha/2}$=1.96 and $Z_{1-\beta}$=1.28

The minimum sample size with a 20% attrition rate was estimated to be 30 (15 in each group).

2.6. Ethical Statement

The study steps, including data collection, data analysis, and reporting the results, were in agreement with the standards settled by the Ethics Committee of Shiraz University of Medical Sciences (IR.SUMS.REC.1400.404). Written consent forms were signed by the participants, and the data were anonymously analyzed and the results were reported back to the participants of the study.

3. Results

Out of the 37 SARS-CoV-2 positive pregnant women, 41% (15/37) were in the second trimester and 59% (22/37) were in the third trimester. Table 1 shows the maternal and newborn characteristics of 37 SARS-CoV-2 positive pregnant women, and their SARS-CoV-2 negative newborn in the second and third trimesters.

Table 1: Maternal and newborn feature comparison by 2nd and 3rd trimesters of pregnancy

Characteristic		Total (n=37)	Trimester		P value
			2nd trimester (n=15)	3rdtrimester (n=22)	
Age (year), median±IQR		30±10	31±7.25	27±10.5	0.04
GA (week), median±IQR		37±4	38±2	37±4.25	0.95
Gravidity, n (%)	1	7 (18.9%)	3 (20%)	4 (18.2%)	0.91
	2	14 (37.8%)	5 (33.3%)	9 (40.9%	
	≥3	16 (43.2%)	7 (46.7%)	9 (40.9%)	
Live birth, n (%)	0	14 (37.8%)	6 (40%)	8 (36.4%)	>0.99
	1	9 (24.3%)	3 (20%)	6 (27.3%)	
	≥2	14 (37.8%)	6 (40%)	8 (36.4%)	
Abortion, n (%)	0	27 (73%)	11 (73.3%)	16 (72.7%)	0.51
	1	8 (21.6%)	4 (26.7%)	4 (18.2%)	
	≥2	2 (5.4%)	0 (0%)	2 (9.1%)	
Still birth, n (%)	0	35 (94.6%)	15 (100%)	20 (90.9%)	>0.99
	1	1 (2.7%)	0 (0%)	1 (4.5%)	
	≥2	1 (2.7%)	0 (0%)	1 (4.5%)	
Preterm birth, n (%)	Yes	15 (40.5%)	5 (33.3%)	10 (45.5%)	0.52
	No	22 (59.5%)	10 (66.7%)	12 (54.5%)	
Delivery type, n (%)	NVD	6 (16.2%)	0 (0%)	6 (27.3%)	0.06
	C/S	31 (83.8%)	15 (100%)	16 (72.75)	
Birth weight (gram), median±IQR		2650±1000	2600±1525	2942±875	0.30
Birth height (centimeter), median±IQR		51±3	50±3	51±3	0.44
1st minute Apgar score, median±IQR		8±1.5	8±2	8±1.25	0.98
5th minute Apgar score, median±IQR		9±1.5	9±2	9±1.25	0.83
Sex, n (%)	Male	21 (56.8%)	8 (53.3%)	13 (59.1%)	0.74
	Female	16 (43.2%)	7 (46.7%)	9 (40.9%)	

GA: Gestational Age; IQR: Inter Quartile Range; NVD: Normal Vaginal Delivery; C/S: Cesarean Section

Table 2: IgG antibody concentrations and COVID-19 severity comparison by 2nd and 3rd trimesters of pregnancy

Characteristics		All (n=37)	Pregnancy trimester		
			2nd trimester (n=15)	3rd trimester (n=22)	P value
Maternal IgG concentration (U/mL), median±IQR		1.3±1.4	1.6±1	1.2±1.125	0.24
Interval between the onset of infection and delivery (week), median±IQR		4±8	11±4	2±3	<0.001
Maternal IgG concentration (U/mL), n (%)	High[a]	27 (73%)	13 (86.7%)	14 (63.6%)	0.15
	Low[b]	10 (27%)	2 (13.3%)	8 (36.4%)	
Cord IgG concentration (U/mL), median±IQR		0.7±0.925	0.7±0.8	0.7±1.04	0.38
Cord IgG concentration (U/mL), n (%)	High[a]	16 (34.2%)	6 (40%)	10 (45.5%)	>0.99
	Low[b]	21 (56.8%)	9 (60%)	12 (54.5%)	
COVID-19 severity, n (%)	Mild and moderate	26 (70.3%)	11 (73.3%)	15 (68.2%)	>0.99
	Severe	11 (29.7%)	4 (26.7%)	7 (31.8%)	

[a]IgG (≥1.1 U/mL); [b]IgG (<1.1 U/mL); IgG: Immunoglobulin G; IQR: Inter Quartile Range

The results revealed no significant difference between the second and third trimesters in terms of GA (P=0.95), gravidity (P=0.91), live birth (P>0.99), abortion (P=0.51), still birth (P>0.99), preterm birth (P=0.52), delivery type (P=0.06), and newborn's birth weight (P=0.30), birth height (P=0.44), first minute Apgar score (P=0.98), fifth-minute Apgar scores (P=0.83), and sex (P=0.74); however, maternal age was significantly higher in 2nd trimester (P=0.04). Mothers' IgG antibody concentrations, newborns' IgG antibody concentrations, and COVID-19 severity in the second and third trimesters are presented in Table 2.

The results showed no significant difference between the second and third trimesters in terms of maternal IgG concentration (P=0.24), cord IgG concentration (P=38), and maternal COVID-19 severity (P>0.99). However, the interval between the onset of infection and delivery was significantly longer in the second trimester as compared with the third trimester (P<0.001).

The correlation between maternal IgG and cord IgG concentrations in the second and third trimesters is depicted in Figure 1A. The correlation between the cord IgG concentration and interval between the onset of infection and delivery in the second and third trimesters is shown in Figure 1B.

The results revealed no significant correlation between cord blood IgG concentrations and maternal IgG concentrations in the second trimester of pregnancy (Pearson's correlation=0.43, P=0.11). However, a significant positive correlation was observed in this regard in the third trimester (Pearson's correlation=0.84, P<0.001).

The results showed no significant relationship between cord blood IgG concentrations and interval between the onset of infection and delivery in the second trimester (Pearson's correlation=0.20,

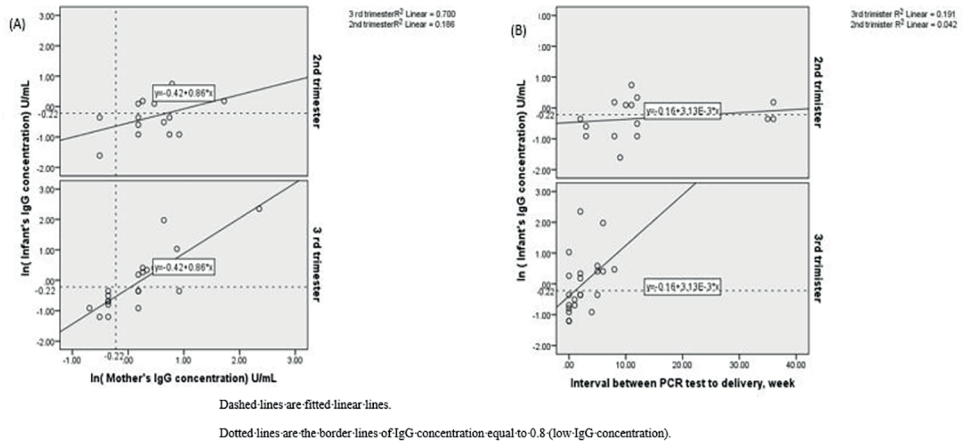

Figure 1: The figure shows the correlations among the cord and maternal IgG antibody concentrations and the onset of COVID-19 infection by 2nd and 3rd trimesters of pregnancy; (A): The correlation between the IgG concentrations of SARS- CoV-2 positive mothers and their negative infants in the 2nd and 3rd trimesters of pregnancy; (B): The correlation between the IgG concentrations of SARS-CoV-2 negative infants and the interval between the PCR+ test result and delivery in the 2nd and 3rd trimesters of pregnancy.

P=0.46). However, a significant positive correlation was observed in this regard in the third trimester (Pearson's correlation=0.44, P=0.04).

The associations between cord IgG and maternal IgG concentrations, COVID-19 severity, and interval between the onset of infection and delivery in the second and third trimesters are presented in Table 3.

In the second trimester, using univariate analysis, the cord IgG concentration was not associated with maternal IgG concentration (cRR (95% C.I); 1.15 (0.94-1.39), P=0.18) and interval between the onset of infection and delivery (cRR (95% C.I); 1 (0.98-1.04), P=0.42); and was the same for multiple analysis (aRR (95% C.I); 1.33 (0.92-1.39), P=0.12 for maternal IgG concentration and aRR (95% C.I); 1.01 (0.99-1.03), P=0.35 for the interval between the onset of infection and delivery). In the third trimester; however, using univariate analysis, higher cord IgG concentrations were associated with higher maternal IgG concentrations (cRR (95% C.I); 2.77 (2.14-3.58) P<0.001) and higher interval between the onset of infection and delivery (cRR (95% C.I); 1.18 (1.02-1.36), P=0.02); and was the same with multiple analysis (aRR (95% C.I); 2.86 (2.27-3.6), P<0.001 for maternal IgG concentration and aRR (95% C.I); 1.23 (1.01-1.51), P=0.03 for the interval between the onset of infection and delivery. Furthermore, the results demonstrated no significant associations between the cord IgG concentration and maternal COVID-19 severity neither in the univariate analysis (cRR (95% C.I); 0.75 (0.39-.1.45), P=0.39 in the second trimester and cRR (95% C.I); 0.78 (0.34-1.76), P=0.55 for the third trimester) nor in the multiple analysis (aRR (95% C.I); 0.68 (0.39-1.19), P=0.25 for the second trimester and aRR (95% C.I); 0.88 (0.09-8.66), P= 0.36 for third trimesters.

Almost 73% (27/37) of the mothers enjoyed high IgG antibody levels, 48% of whom (13/27) were in the second trimester and 52% (14/27) were in the third trimester. The association between the levels of maternal IgG and cord IgG in the second and third trimesters are presented in Table 4.

The results of both univariate and multiple analyses indicated that higher levels of maternal IgG were associated with higher levels of cord IgG (cRR (95% C.I); 2.43 (1.12-5.25), P=0.02 and aRR (95% C.I); 2.31 (1.05-5.09), P=0.03, respectively) in the third trimester. However, the results of univariate and multiple analyses showed no significant associations between the maternal

Table 3: The cord IgG concentration association with maternal IgG concentration, interval between the onset of infection and delivery, and COVID-19 severity by 2nd and 3rd trimesters of pregnancy

Characteristics		Univariate analysis		Multiple analysis	
		2nd trimester, n=15	3rd trimester, n=22	2nd trimester, n=15	3rd trimester, n=22
Dependent variable		Cord IgG concentration, U/mL	Cord IgG concentration, U/mL	Cord IgG concentration, U/mL	Cord IgG concentration, U/mL
Independent variable		cRR (95% CI)	cRR (95% CI)	aRR* (95% CI)	aRR* (95% CI)
Maternal IgG concentration, U/mL		1.15 (0.94-1.39)	2.77 (2.14-3.58)	1.33 (0.92-1.39)	2.86 (2.27-3.6)
Interval between the onset of infection and delivery (week)		1 (0.98-1.04)	1.18 (1.02-1.36)	1.01 (0.99-1.03)	1.23 (1.01-1.51)
COVID-19 severity	Mild and moderate (ref)	1 (.-.)	1 (.-.)	1 (.-.)	1 (.-.)
	Severe	0.75 (0.39-1.45)	0.78 (0.34-1.76)	0.68 (0.39-1.19)	0.88 (0.09-8.66)

*Adjusted on maternal age; [c]RR: crude Rate Ratio; [a]RR: adjusted Rate Ratio; IQR: Inter Quartile Range; 95% C.I: 95% confidence interval

Table 4: The association between the IgG levels of 37 SARS-CoV-2 positive pregnant women and their 37 SARS-CoV-2 negative newborns in the 2nd and 3rd trimesters

Characteristics		Univariate analysis						Multiple analysis	
		2nd trimester, n=15			3rd trimester, n=22			2nd trimester, n=15	3rd trimester, n=22
Dependent variable		Cord IgG level, n (%)			Cord IgG level, n (%)			Cord IgG level, n (%)	Cord IgG level, n (%)
Independent variable		High[a]	Low[b]	cRR (95% CI)	High[a]	Low[b]	cRR (95% CI)	aRR* (95% CI)	aRR* (95% CI)
Maternal IgG level	High[a]	6 (46.2%)	7 (53.8%)	1.92 (0.46-8.12)	10 (71.4%)	4 (28.6%)	2.43 (1.12-5.25)	1.97 (0.42-9.22)	2.31 (1.05-5.09)
	Low[b](ref)	0 (0%)	2 (100%)		0 (0%)	8 (100%)			

[a]IgG ≥1.1 U/mL; [b]IgG <1.1 U/mL; *Adjusted on maternal age; IQR: Inter Quartile Range; [c]RR: crude Rate Ratio; Arr: Adjusted Rate Ratio; 95% C.I: 95% confidence interval

and cord IgG levels in the second trimester (cRR (95% C.I); 1.92 (0.46-8.12), P=0.37 and aRR (95% C.I); 1.97 (0.42-9.22), P=0.40, respectively). All the newborn born from low maternal IgG levels had low cord IgG levels in both trimesters.

4. Discussion

Based on the study findings, pregnant women with COVID-19 were the same in the 2nd and 3rd trimesters regarding GA at delivery, gravidity, live birth, abortion, still birth, preterm birth, and delivery type; however, maternal age was significantly higher in the 2nd trimester. Additionally, the exposed but negative newborns were the same regarding birth weight, birth height, first- and fifth-minute Apgar scores, and sex. Maternal IgG concentrations, cord IgG concentrations, and COVID-19 severity were also similar in the 2nd and 3rd trimesters. However, the interval between the onset of infection and delivery was longer in the 2nd trimester. Furthermore, the cord IgG concentration was positively associated with the maternal IgG concentration and the interval between the onset of infection and delivery, but not with the severity of COVID-19 in the 3rd trimester. In addition, efficient trans-placental IgG antibody transfer occurred in the 3rd trimester of pregnancy. Nonetheless, no significant associations were observed between cord IgG and maternal IgG concentrations, interval between the onset of infection and delivery, and COVID-19 severity in the 2nd trimester. The results also indicated no significant association between the cord IgG and maternal IgG levels in the 2nd trimester of pregnancy, which implied that no immunity was gained in this trimester. Therefore, vaccination was recommended to be done in late pregnancy in order to make newborns effectively immune against COVID-19. Also, it is highly recommended to follow the newborns in order to investigate the potential immunity caused by COVID-19 infection during pregnancy.

In agreement with our results, no association was seen with COVID-19 severity (14). Additionally, studies have revealed a positive correlation between maternal and cord IgG concentrations, confirming infants' effective immunity in late pregnancy. This finding accentuated the current findings in which high levels IgG antibody (≥1.1 U/mL) resulted in significantly high level cord IgG(≥1.1 U/mL) (15-17). Previous studies have shown that babies born from mothers with very low IgG levels had low cord IgG levels resulted in no efficient immunity, especially in the 2nd trimester of the pregnancy. This was in agreement with the our results in which no efficient immunity was produced in the 2nd trimester of pregnancy (15, 18, 19).

4.1. Strength and Limitation

One of the limitations of the current work was that some patients with mild or moderate COVID-19 symptoms did not seek treatment at the recruitment centers; this may have led to an increased probability of underestimation of the reports. Another limitation of the present work was our shortage of data on post-discharge outcomes. Reviewing medical record was also limited to the assessment of COVID-19 symptoms during pregnancy. However, the strength of the present study was its cohort design including causality criteria, especially temporality, intact eligibility criteria set for the patients to be included in the analysis, and precise observation during the follow-up, which makes the results more generalizable and less prone to bias. Controlling underlying diseases and age, as the well-known risk factors of COVID-19, could also minimize biases in this study. Furthermore, the role of GA in mother-to-child antibody transmission was evaluated, suggesting potential vaccination strategies for pregnant women.

5. Conclusions

COVID-19 infected pregnant women and their newborns were the same in the 2nd and 3rd trimesters of pregnancy regarding maternal and neonatal characteristics; however, maternal age was significantly higher in the 2nd trimester. In addition, maternal IgG concentration, cord IgG concentration, and COVID-19 severity were the same in the 2nd and 3rd trimesters; however, interval between the onset of infection and delivery was higher in the 2nd trimester. After adjusting on maternal age, in the late pregnancy, Cord IgG concentration was positively associated with maternal IgG concentration and interval between the onset of infection and delivery. Also, high levels of IgG antibody (≥1.1 U/mL) resulted in significantly higher level of cord IgG (≥1.1 U/mL), which implied that immunity was gained in the 3rd trimester. Therefore, vaccination was recommended to be done in late pregnancy in

order to make newborns effectively immune against COVID-19. Also, it is highly recommended to follow the newborns in order to investigate the potential immunity caused by COVID-19 infection during pregnancy.

Acknowledgment

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Ethical Approval

All the study stages including data collection and analysis and reporting the results were in accordance with the standards approved by the Ethics Committee of Shiraz University of Medical Sciences with the code of IR.SUMS.REC.1400.404. Also, informed consent form was taken from the patients, the data were analyzed anonymously and the results were reported to the study participants.

Authors' Contribution

Maryam Kasraeian: Contributed to the conception and design of the study, drafting the article and revising it critically for important intellectual content, and final approval of the version to be submitted. Maryam Zarekhafri: Contributed to the conception and design of the study, drafting the article and revising it critically for important intellectual content. Homeira Vafaei: Contributed to the conception and design of the study, drafting the article and revising it critically for important intellectual content. Behrouz Gharesi-Fard: Contributed to data acquisition and drafting the article. Azam Faraji: Contributed to the conception and design of the study, drafting the article and revising it critically for important intellectual content. Nasrin Asadi: Contributed to the conception and design of the study, drafting the article and revising it critically for important intellectual content. Asieh Seraj: Contributed to data acquisition and drafting the article. Shaghayegh Moradi Alamdarloo: Contributed to data acquisition and drafting the article. Shohreh Roozmeh: Contributed to data acquisition and drafting the article. Khadijeh Bazrafshan: Contributed to data acquisition and drafting the article. Marjan Zare: Contributed to the conception and design of the study, analysis and interpretation of data, drafting the article and revising it critically for important intellectual content. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work, such as the questions related to the accuracy or integrity of any part of the work.

Conflict of Interests: None declared.

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